UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/035,688	11/08/2001	Laurie H. Glimcher	HUI-037CN	3399

959 7590 10/06/2003

LAHIVE & COCKFIELD
28 STATE STREET
BOSTON, MA 02109

EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	5

DATE MAILED: 10/06/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/035,688	GLIMCHER ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 32-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 32-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Specification

The description of the drawings refers to Figures 2B and 2C (pg 3, line 25 and 28) which should be Figures 1B and 1C.

The disclosure is objected to because the pages are not numbered. A substitute specification with page numbers is required.

The computer readable format of the Sequence listing has been entered. A paper copy of the Sequence listing cannot be found. A statement that the paper copy and computer readable format of the Sequence listing are the same cannot be found. Please file a paper copy of the Sequence listing and a statement that the paper copy and computer readable format of the Sequence listing are the same.

Priority

Application 09/181716 cannot be found at this time to assess applicants' claim for priority.

The first line of the specification will need updated as necessary indicating priority application 09/181,716 has been abandoned.

Claims 2-31 have been canceled. Claims 1 and 32-51 are pending and under consideration in the instant office action.

Claim Objections

Claim 38 is objected to because "transgenic" is misspelled. Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1 and 32-51 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific or substantial asserted utility or a well-established utility.

Claims 1 and 32-44 are directed toward a transgenic mouse having a disruption of NFATp and NFAT4. Claims 45-48 are directed toward using the mouse to test for compounds that regulate Th2 activity.

The specification teaches such mice having increased Th2 cytokine levels, slightly increased Th1 cytokine levels, increased IgE and IgG1, and slightly increased IgG2a and 2b levels (Example 3). The specification states that by inhibiting NFATp and NFAT4 activity using a compound, an increased Th2 activity may occur. Increased Th2 activity may be useful in treating disease states including encephalomyelitis (EAE), type I diabetes or rheumatoid arthritis (RA) in which an increased Th2 activity is desired (Section III, A).

Oukka (Immunity, 1998, Vol. 9, pg 295-304) taught mice having a disruption in NFAT4 had impaired development of CD4 and CD8 SP thymocytes and peripheral T cells and hyperactive peripheral T cells. Hodge (Immunity,

1996, Vol. 4, pg 397-405) taught mice having a disruption in NFATp had an enlarged spleen, hyperproliferation of B and T cells and an increase in Th2 activity. The art at the time of filing did not teach the NFAT4 or NFATp deficient mice were a model for disease or teach how to use the mice to screen compounds. Since the time of filing, Rengarajan (Immunity, 2000, Vol.12, pg 293-300) and Ranger (Immunity, 1998, Vol. 9, pg 627-635) taught mice having a disruption in both NFATp and NFAT4. The art since the time of filing does not teach the mice are a model for disease or teach how to use the mice to screen compounds.

The mouse claimed does not have a specific utility. The mice claimed do not have a phenotype of a specific disease. The disruption in NFATp or NFAT4 does not correlate to any disease. The specification does not teach how to use a mouse that has swollen glands, swollen spleen, swollen eyelids, inflamed lungs, increased T cells, compromised FasL expression or defective apoptosis as a model of disease (claims 33-44). Using the mouse to identify compounds that regulate Th2 activity is not specific to the mouse claimed because the method may be performed using treated and non-treated wild-type mice. In other words, using a mouse already having increased Th2 activity to find compounds that increase the Th2 activity is not specific to that mouse because wild-type mice can be used to find compounds that increase Th2 activity. Likewise, using a mouse having increased Th2 activity to find a compound that decreases Th2 activity can also be using wild-type mice. Therefore, using the mouse to identify compounds

that regulate Th2 activity is not specific to that mouse, and the mouse claimed does not have a use that is specific to any disease.

The mouse claimed does not have a substantial utility. The specification states the mouse is used to test compounds that modulate Th2 activity by modulating NFATp and/or NFAT4 (Section III, line 3-6); however, the mice do not express NFATp or NFAT4. Therefore, compounds that modulate NFATp or NFAT4 cannot be found using the mice because NFATp and NFAT4 are not expressed in the mice. The mice of the invention have an increased Th2 activity; however, the specification does not provide a use for identifying a compound that increases Th2 activity in a mouse already having an increased Th2. Therefore, using the mouse to identify compounds that modulate NFATp, NFAT4 or Th2 activity is not substantial.

Claim 49 is included because it is directed toward making the mouse, which lacks utility for reasons above.

Claims 50-51 are directed toward cells having a disrupted NFATp and NFAT4 gene. Claims 50-51 are included because the cells lack a specific and substantial utility for the reasons above.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and

use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 32-51 also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Upon overcoming the above rejection and describing a use for the mouse claimed, the specification does not enable making or using a transgenic having the disruptions as claimed with a wild-type phenotype as encompassed by the claims. The transgenics throughout Examples 1-3 do not have wild-type phenotype; however, claim 1 encompasses wild-type phenotype. The specification does not provide any use for a transgenic as claimed having a wild-type phenotype. The specification describes the phenotypes of the mice claimed in Example 1 (¶ 4). Therefore, the independent claims should be limited to mice having a phenotype described in the specification.

Claims 50 and 51 encompass mice and rats. "Murine" encompasses mice and rats (http://www.m-w.com/cgi-bin/dictionary?book=Dictionary&va=murine). The specification does not teach how to make murines having a disruption in NFATp and NFAT4 other than mice. The state of the art at the time of filing was such that embryonic stem (ES) cell technology had only been successful in mice. Wagner (May 1995, Clin. and Experimental Hypertension, Vol. 17, pages 593-605) and Mullins (1996, J. Clin. Invest., Vol. 98, pages S37-S40) taught germline

transmission of ES cells has not been demonstrated in species other than mice and the growth of ES cells from species other than mice is unreliable. Wall (1996, Theriogenology, Vol. 45, pg 57-68) taught transgene expression and the physiological result of such expression in livestock was not always accurately predicted in transgenic mice (page 62, line 7). The specification fails to provide sufficient guidance to make transgenics other than mice by teaching obtaining ES cells in species other than mice. The specification does not teach the nucleic acid sequence of the rat NFATp or NFAT4 gene or correlate the NFATp or NFAT4 gene in mice to the NFATp or NFAT4 gene in rats. The specification does not teach how to make knockout rats or correlate making knockout mice to making knockout rats. Therefore, the specification does not provide adequate guidance for one of skill in the art to make a murine cell having a disruption of NFATp and NFAT4 in any species other than mice.

Claim 49 is directed toward a method of making a transgenic mouse using any exogenous nucleic acid molecule comprising a portion of NFATp and NFAT4 having one or more deletions in one or more exons introduced into any ES cell. The claim does not require using mouse ES cells which is essential to making a mouse. The claim does not require the mouse have a phenotype that differs from wild-type, which is required for reasons cited above. The specification does not teach introducing both constructs into the ES cell at the same time as claimed; the only means of making the mice claimed is breeding a knockout NFATp mouse with a knockout NFAT4 mouse.

Claims 45-48 are directed toward methods of screening compounds that regulate Th2 activity using the mouse of the invention. The purpose of the method is to determine compounds that modulate NFATp or NFAT4 (Section III, see especially 3rd ¶, 1st sentence). Step (c) requires evaluating the Th2 activity in a transgenic mouse given a compound compared to a second transgenic mouse. While one of skill could readily evaluate and compare the Th2 activity in the mice, the specification does not teach how the comparison leads to identifying compounds that regulate Th2 activity. Such a disclosure is essential to determine compounds that modulate NFATp or NFAT4. Without such a disclosure, the specification does not provide adequate guidance for one of skill to determine compounds that modulate NFATp or NFAT4.

Claims 32-51 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification as originally filed did not support the breadth of any "nucleic acid molecule" that functionally disrupts an NFATp or NFAT4 gene; the original claims and specification are limited to DNA that disrupts the NFATp or NFAT4 genes.

The phenotypes in new claims 33-44 cannot be found in Examples 1-3 or on pg 36-41 as stated in the preliminary amendment filed 11-8-01.

The steps of claim 45 are not disclosed in Examples 1-3 or on pg 36-41 as stated in the preliminary amendment filed 11-8-01. The specification does not teach administering a compound to one mouse but not the other or comparing the "Th2 cell activity" of each mouse as newly claimed.

The amino acid sequences of SEQ ID NO:1-3 are not found in Examples 1-3 or on pg 36-41 as stated in the preliminary amendment filed 11-8-01. Administering the amino acids to mice as claimed was not contemplated in the specification as originally filed. See section of specification labeled "iii. NFATp-Derived Peptidic Compounds".

The steps in claim 49 cannot be found in Examples 1-3 or on pg 36-41 as stated in the preliminary amendment filed 11-8-01. Example 1 describes cross breeding a mouse lacking NFATp with a mouse lacking NFAT4 (¶ 2), not introducing NFATp and NFAT4 knockout constructs into a mouse ES cell as claimed.

The breadth of "murine" in claim 50 was not contemplated in Examples 1-3 or on pg 36-41 as stated in the preliminary amendment filed 11-8-01.

The types of cells in claim 51 were not contemplated in Examples 1-3 or on pg 36-41 as stated in the preliminary amendment filed 11-8-01.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 32-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "exogenous" (1, 32, 49) is indefinite because the term is relative. It cannot be determined whether the DNA is exogenous to mice as a species or to the mouse as an individual.

The term "characterized" in claims 33-36 is indefinite because it is unclear whether the mouse has the trait or has qualities of the trait.

The metes and bounds of what applicants consider "memory/activated phenotype" (claim 38) cannot be determined.

It is unclear whether claim 39 is limited to decreased FasL expression or whether the claim encompasses normal FasL expression level of a "compromised" FasL protein.

The metes and bounds of what applicants consider "IL-4 dependent immunoglobulin isotypes" (claim 43) cannot be determined.

The metes and bounds of what applicants consider "calcineurin-interacting region of NFATp or NFAT4" (claim 45) cannot be determined.

"[S]aid peptidic compound" in claim 48 lacks antecedent basis.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

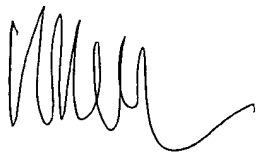
Questions of formal matters can be directed to the patent analyst, Dianiece Jacobs, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-3388.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

Michael C. Wilson



MICHAEL WILSON
PRIMARY EXAMINER